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Key Characteristics: A New Approach to Identifying Potential Toxicants, with Martyn Smith

Ashley Ahearn

It would be nearly impossible using current methods to test all the chemicals in use for toxic effects. So how do we prioritize which ones to study? In this podcast, Martyn Smith describes how he and his colleagues are developing lists of "key characteristics" shared by toxicants that cause specific adverse health effects, such as cancer or reproductive toxicity. Risk assessors can use this information to predict the toxicity of other chemicals in an organized, systematic way. This approach may be useful in prioritizing chemicals for more detailed evaluation. https://doi.org/10.1289/EHP5776

NARRATOR [00:00:00]: *EHP* presents "The Researcher's Perspective."

[Theme music]

AHEARN [00:00:10]: It is "The Researcher's Perspective." I am Ashley Ahearn.

We're exposed to thousands of chemicals every day, but only a small fraction of these chemicals have been tested for toxicity.

It would be nearly impossible using current methods to test all the chemicals in use for toxic effects. So how do we prioritize which ones to study? And how do scientists organize the vast amounts of existing data in order to define chemicals as, say, carcinogenic or toxic to human reproduction?

Dr. Martyn Smith has been tackling that problem with a group of scientists from a wide range of academic and research backgrounds.

Smith is a professor of toxicology at the University of California, Berkeley, School of Public Health, where he also directs the Superfund Research Program. He and his colleagues put together a list of 10 key characteristics associated with human carcinogens.[1]

Now they have compiled two new lists of key characteristics of chemicals that are toxic to male[2] and female[3] reproduction.

Dr. Smith, welcome to "The Researcher's Perspective."

SMITH [00:01:07]: Thank you for inviting me.

AHEARN [00:01:09]: Okay, so take me back to when you and a group of your colleagues put together a list of the 10 key characteristics of human carcinogens. Tell me, how did you do it? I mean, I am sitting here picturing a bunch of scientists sitting around a table with a whiteboard and sort of arguing about which biological pathways are the most important in, say, causing cancer.

SMITH [00:01:26]: Well, that's exactly what happened. The IARC, International Agency for Research on Cancer, convened a whole group of people in Lyon in 2012. They sat around literally almost with a blackboard and made a list, actually, of 26 things that they thought were important in cancer development. And so, we asked a statistician in the room, how many do we need and how many should we have? And he said 10. So we tried to hone that 26 into 10, and there was a lot of debate and took two meetings to do that. So basically, it was all done by expert committee and argument.

AHEARN [00:02:03]: I mean, it just seems to me like as we were saying with thousands of chemicals on the market there is just this overwhelming amount of inputs without a way to really sift and sort for what is most relevant and useful if we're trying to protect public health.

SMITH [00:02:15]: Yeah, there is. There is this issue of how do you prioritize what to look at. And some people say, well, we just, you know, work on classes, but that really is unsatisfactory to most chemists, because they know that just changing the structure very slightly will change the properties of the chemical. So how do you evaluate all of these chemicals quickly? And this is a problem we've had for, you know, several years now, and we're just hoping that the key characteristics concept can help us with this by looking at thousands of chemicals in a particular, uniform, standardized way.

AHEARN [00:02:52]: So tell me about the characteristics that made the list. What properties does a chemical need to have?

SMITH [00:02:58]: Yeah so, when I talk about this list some people say, well, they are obvious, and kind of that's the point, actually. They are like 10 things that everybody agrees on are important.

We started off with the sort of simple things, like damaging DNA and being a highly reactive compound. They were key characteristics 1 and 2. But I think what the next group show is that there were a whole group of effects that chemicals have that are important in cancer that are often ignored in evaluations by things like the Ames test or typical tests that are used, which mostly measure DNA damage. So things like inflammation and suppression of the immune system or alterations to the telomeres of the, of the chromosomes which make cells live longer, or inhibition of programmed cell death like apoptosis. So those things all, all made the list, and they are not usually considered often in looking at whether a chemical is a cancer hazard or not.

AHEARN [00:04:06]: Dr. Smith, how do you think our chemical exposures are affecting human reproductive health now?

SMITH [00:04:12]: Well, that's a controversial topic that I have to say that I am not a leading expert on. I just really, what I did here is convene some of the world's experts in that area and asked them to think about this. But in the opening paragraphs of these two articles[2,3] in *Environmental Health Perspectives*, we sort of lay the groundwork of how fertility and other forms of reproductive health are being injured by environmental chemicals, and that the evidence for this is increasing and that things like testicular cancer in young men is increasing and some of the other issues with fertility are quite clear and the role of environmental chemicals is becoming clearer and clearer. And we do lay that out at the beginning of both articles.

AHEARN [00:04:59]: Is that part of why you wanted to apply your list-making approach to chemicals that might be affecting human reproductive health?

SMITH [00:05:06]: Yes, I mean, in part, that was one of the reasons why we did. It is also, I have to say, a focus of the California EPA because of Proposition 65.[4] They make lists of chemicals which are carcinogenic and lists of chemicals which are harmful to reproduction, and so they had an interest in developing these key characteristics for their use in Proposition 65 evaluation.

AHEARN [00:05:31]: OK, so if I line these lists up next to each other, the carcinogens list and the toxicity to male and female reproduction lists, tell me what are the common denominators here, Dr. Smith?

SMITH [00:05:42]: Well, the common effects are things like damage to the DNA, which is called genotoxicity; epigenetic

alterations, which are where there's no change in the DNA sequence but there is an alteration in gene expression; alterations in hormone levels and in the function of receptors for those hormones; and also things like oxidative stress and inflammation.

Now, we know that all of those things I just listed are bad events, are things that are harmful; does not matter whether it is in the reproductive tract or if it is in the breast tissue or the prostate tissue—it does not matter. So it is not surprising that these commonalities exist in terms of having harmful effects on different tissues. It just so happens that to harm reproduction they occur in the reproductive tract of either the male or the female, whereas in producing cancer they occur in epithelial cells or in stem cells in the bone marrow or other tissues to produce cancers.

AHEARN [00:06:45]: I could not help but notice you made different lists of the characteristics of chemicals that are toxic to male reproduction versus female reproduction. And I am wondering, why is that and how are those two lists different?

SMITH [00:06:56]: Yes, it is interesting you brought that up. I mean when we initially convened this group of people, we intended really to make a list of reproductive toxicants. So key characteristics of just general reproductive toxicants. But the experts in the room told me that, you know, male and female are very different and we needed to make two separate listings.

And so we make two separate committees, and they somewhat overlapped but mostly independently came up with their lists. And it is quite interesting to compare them now. There are some that are the same, pretty much the same, and there are others that are quite different. So I, I was following expert guidance really that we needed to have two sets of characteristics here.

AHEARN [00:07:43]: Now, why would there be more characteristics on the female list? There are 10 when there are 8 on the male list.

SMITH [00:07:49]: Yeah that's interesting, too. I mean, the female group added cell–cell interactions and effects on microtubules and effects on mitochondria, which were not in the male group. And that may be just uniqueness of the female reproductive tract. The female group also decided to put modulation of the immune system—be it inflammation, which is promotion of the immune system, or immunosuppression, dampening down of the immune system—into one category, whereas the males added inflammation as a separate group.

So there are lots of similarities, they are in different order and some differences between the two, but there is an awful lot of similarities. And if a particular agency wanted to unify these to simplify it, that would be perfectly fine. This was just really the way it came out from the expert groups acting independently and acting on their own belief systems, really, and I just let the process take its course.

AHEARN [00:08:52]: So let's, for the sake of experimentation here, let's take a given chemical, atrazine, for example. It is an herbicide that's widely used in the U.S.[5] though it is been banned in Europe because of human health concerns.[6] And I want to know, how would you use your list of characteristics to classify this chemical, Dr. Smith?

SMITH [00:09:08]: Well, I wouldn't do that on my own. You could do that, but that would just be a, be a lot of work, and it'd also be a personal opinion. So I mean, what we've produced here is really an approach to doing that.

So what you would do is, you would take the key characteristics, and you would have a set of search terms based around all of those key characteristics, and you would systematically search the literature using whatever programs you want to use, and you'd collect all the literature. There are then programs which will organize that literature into groups related to the key characteristics. So you could get al.l the papers related to genotoxicity of atrazine, for example, and put them into one group.

And then what I would do is, I'd convene a group of experts who understood all of these different characteristics and probably knew a little bit about atrazine. I'd put them together in a room and have them evaluate that material. I would actually let them do that for several weeks, then put them in a room to debate it and have them vote about how strong they thought the evidence was for each of the key characteristics. And then I'd add that into what we know about the epidemiology and the animal studies of atrazine in making an evaluation.

AHEARN [00:10:24]: Dr. Smith, are you the kind of person that makes grocery lists and to-do lists?

SMITH [00:10:27]: Yes, all the time. [Laughs] I am a list type person. I am actually so poorly organized, otherwise I'd just go crazy.

AHEARN [00:10:38]: So you are basically doing this for the entire public health community now.

SMITH [00:10:42]: [Laughs] Yes, I am imposing my own personal organization onto others.

AHEARN [00:10:47]: Well, it seems like you have some excellent, and willing, accomplices in figuring how to do this. It is really cool to see the process.

SMITH [00:10:53]: Yes, I've been really surprised and actually honored; everybody's basically said yes if they could come to any of these meetings, and they have contributed their time for free. The California EPA has paid their travel, but nobody's been, earned any money out of it, and they have all devoted their time, they have been on conference calls every two weeks early in the morning. We've involved Japanese scientists, European scientists, and many others. I am very grateful for their time.

AHEARN [00:11:20]: Now, I would think that this approach, you know, listing the key characteristics of chemicals that lead to certain health outcomes, could be applied to a lot of different public health problems. What are you most excited about in terms of where this process, this procedure, can be applied in the future?

SMITH [00:11:35]: Well then, the next set of key characteristics we're going to develop is going to be for neurotoxicity and developmental neurotoxicity, and Pamela Lein at UC Davis is going to lead that. And we already have a meeting planned for September and hopefully will produce a list of key characteristics for both neurotoxicants and developmental neurotoxicants. And a bit later in the year, we're planning to do cardiotoxicants, and Weihsueh Chiu has agreed to lead that.

And we then plan to follow up on this concept of, well, maybe there are such things as bad chemicals if you, if you like, or harmful chemicals. Which there could be a set of key characteristics of harmful chemicals—ones which produce cancer, reproductive harm, endocrine disruption, cardiotoxicity, or neurotoxicity—that we could develop a set of key characteristics which would be all-encompassing for those things. And then develop a set of tests and assays for those things which are mostly, basically what people die of in most countries and that we could lower the burden of chronic disease by finding out the truly bad chemicals and bad actors which may be contributing to that.

And so I am hoping that these lists will lead to tests, assays, and even computer programs and ways of using artificial intelligence to predict which are the most harmful chemicals, and then we can prioritize and really act. So, go to action much quicker rather than waiting for all the information. The most frustrating thing, I think, at the moment for regulators and for people who are concerned members of the public is the frustration of, like, where's the information that we could use to really make these decisions? And I think what I am trying to do here is really speed up the process so to provide the scientific information for others to make the decisions.

AHEARN [00:13:37]: Dr. Smith, thank you so much for joining me.

SMITH [00:13:39]: Thank you for inviting me.

AHEARN [00:13:41]: Dr. Martyn Smith is a professor of toxicology at the UC Berkeley School of Public Health and director of the Superfund Research Program there, which is funded by the NIEHS. He's the coauthor of two commentaries in *EHP* that describe key characteristics that can be used to identify potential new reproductive toxicants for both men[2] and women.[3]

[Theme music]

I am Ashley Ahearn. Thanks so much for listening to "The Researcher's Perspective."

The views and opinions expressed in this podcast are solely those of our guest and do not necessarily reflect the views, opinions, or policies of Environmental Health Perspectives *or the National Institute of Environmental Health Sciences*.

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